Trihalomethanes in Drinking Water and Human Colorectal Cancer[1,2]

Charles E. Lawrence, *Ph.D.*,[3] **Philip R. Taylor,** *M.D., S.M.*,[3,4]
Bruce J. Trock, *M.P.H.*,[3,5] *and* **Andrew A. Reilly,** *Ph.D.*[3,6]

ABSTRACT—The relation of trihalomethanes (THM) to colorectal cancer was evaluated. A total of 395 colorectal cancer deaths among white women teachers in New York State was compared to an equal number of deaths of teachers from noncancerous causes. Cumulative chloroform ($CHCl_3$) exposure was estimated by the application of a statistical model to operational records from the individual water treatment facilities that served the home and work addresses of each study subject during the 20 years prior to death. The odds of exposure to a surface source containing little or no THM was no greater for cases than for controls. The odds ratio=1.07; the 90% confidence interval= 0.79-1.43; and the P=.68. The distribution of $CHCl_3$ exposure was not significantly different between cases and controls (rated by Wilcoxon signed rank statistic=−0.52; P=.60). No effect of cumulative $CHCl_3$ exposure on outcome was seen in a logistic analysis controlling for average source type, population density, marital status, age, and year of death (likelihood ratio test statistic=0.047; P=.83).—JNCI 1984; 72:563-568.

The potential carcinogenic impact of THM has been a matter of controversy since Rook (*1*) demonstrated in 1974 that the formation of THM is a consequence of water chlorination. THM, particularly chloroform ($CHCl_3$), are widely present in chlorinated drinking waters and correlate strongly with increasing organic content of raw surface waters (*2, 3*).

Observations from animal studies (*4-7*) prompted a large number of epidemiologic investigations seeking to determine whether $CHCl_3$ or other chlorinated organics in drinking water are associated with elevated cancer risk. Significant positive correlations were found most often for cancers of the large intestine, rectum, and bladder (*8-12*). Those studies were largely ecologic or indirect and used aggregate mortality data and either categorical exposure variables (e.g., chlorinated vs. nonchlorinated) or present-day $CHCl_3$ concentrations as indicators of past exposure. Recent studies have utilized either a case-control or a cohort approach in an attempt to obtain more reliable data. These studies have also demonstrated positive correlations of $CHCl_3$ exposure with gastrointestinal and bladder cancers (*13-16*).

The study described here utilizes case-control sampling, but it differs from the previous studies in several important ways. First, sources of exposure were ascertained for all cases and controls through exhaustive tracing of each individual's places of residence and places of work for 20 years prior to death. Second, $CHCl_3$ exposure from each source was estimated by the application of a statistical model to water treatment data specific for the time and place of exposure. Thus a cumulative $CHCl_3$ dose could be estimated for each study subject. Finally, the study was limited to teachers. This restriction minimized differences in a number of unmeasured variables and, we believe, resulted in a far greater homogeneity of cases and controls with respect to potential confounding variables such as socioeconomic status and occupation than in previous studies.

METHODS

Patient population.—The TRS includes all public school teachers in New York State with the exception of New York City. Between 1962 and 1978 a total of 14,524 deaths occurred among TRS members. Of the deaths, 12,966 occurred in New York and were successfully matched with State vital records. From this group 726 male and female deaths due to cancer of the colon or rectum [codes 153.0-153.9 and 154.0-154.9 of the International Classification of Diseases adapted for use in the United States (8th revision)] were identified on the basis of death certificate data.

Restricting the study to women reduced the number to 590, and an additional restriction to the central geographic corridor within the State based on place of death (excluding the north and southwest) further decreased the number of cases to 442. This restriction was imposed after a random survey of water treatment records in the State found records in the north and southwest portions to be generally less reliable than those in other areas. The study was restricted to white women by the elimination of 7 nonwhites. Five cases were excluded because the tumor registry report indicated cancer other than colon or rectum cancer, and

ABBREVIATIONS USED: THM=trihalomethanes; TRS=New York State Teachers' Retirement System.

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[3] Statistical and Computer Science Laboratory, Center for Laboratories and Research, State of New York Department of Health, Office of Public Health, Tower Building, The Governor Nelson A. Rockefeller Empire State Plaza, Albany, N.Y. 12201.
[4] Harvard School of Public Health, Boston, Mass. 02115.
[5] The Johns Hopkins School of Hygiene and Public Health, Baltimore, Md. 21205.
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35 cases were excluded because of insufficient exposure information or because the subject had resided at some time in New York City.

Analysis was thus based on data from 395 cases, of which 319 were colon and 76 rectal cancers. Review of hospital medical records of 185 cases turned up no mention of ulcerative colitis or familial polyposis in any of these cases. Of the 395 cases, 331 (84%) were histologically confirmed; 29 (7%) were diagnosed by X-ray or surgical observation, and 35 (9%) were diagnosed by physical examination or symptomatology.

From the pool of all TRS deaths occurring between 1962 and 1978 from causes other than cancer, 395 female controls were selected to match the subject cases in age and year of death (±2 yr). Restriction and exclusion criteria similar to those for cases were applied except that individuals with any tumor reported to the tumor registry were excluded as controls. When multiple matches satisfied these criteria, the control was randomly selected.

The number and causes of death among controls were the following: 166 from ischemic heart disease; 79 from cerebrovascular disease; 34 from circulatory system disorders; 24 from digestive system disorders; 17 from respiratory troubles; 13 each from motor vehicle accidents or endocrine-nutrition-metabolic disorders; 11 from nervous system disorders; 8 each from hypertensive disease or other accidents; 4 each from suicide or genitourinary disorders; 3 each from mental disorders, musculoskeletal system disorders, or violence; 2 from infections; and 1 each from disease of the blood, congenital anomalies, or an ill-defined condition.

Exposure data.—Residence and employment information for each subject for the 20-year period prior to death was collected without knowledge of disease outcome to determine the sequence of home and work addresses and the number of years spent at each address. Information was compiled from records at TRS and local school districts, city and telephone directories, tax rolls, marriage records, and billing records of water departments. The effectiveness of the search is shown in table 1.

The results of a survey for THM in 174 water systems (*17*) in New York State supplied exclusively by surface water were utilized to develop a statistical model to estimate $CHCl_3$ concentrations during any given year. Statistically significant predictor variables in the model were limited to pre-chlorine and post-chlorine dose, chlorine residual, and type of water source (*see* "Appendix" for details).

TABLE 1.—*Information characteristics of cases and controls* (n=*394 each*)

Parameter	Age, yr		Duration of history			
			Residence and work		Water treatment	
	Cases	Controls	Cases	Controls	Cases	Controls
Mean	69.7	69.5	19.9	19.9	19.7	19.6
Maximum	94	94	20	20	20	20
Minimum	28	28	10	8	10	6
SD	11.8	11.8	0.04	0.05	1.08	1.50

Operational records were searched for all individual water treatment facilities serving the home and work addresses for each study subject during the 20-year period (table 1). Water system distribution maps were frequently consulted to confirm the source of supply to a specific address. Records of water treatment during July and August for each year of exposure were used as a data base because July and August were the months of the THM survey. The average daily values for chlorine dose and residual for these months were used as average daily values for the year.

Each individual's cumulative $CHCl_3$ exposure over the 20-year period was summarized as follows:

$$\sum_{j=n-19}^{n} \sum_{i=0}^{m} W_{ij} E_{ij},$$

where j indexes the year of exposure during the 20-year period (n=yr of death), m is the number of surface sources of exposure in a given year, W_{ij} is the proportion of total exposure during year attributable to water supply i, and E_{ij} is the $CHCl_3$ exposure during year j if due entirely to water supply i.

The estimate of exposure over 20 years required the following assumptions: average consumption of 2 liters of water daily, divided equally between home and work, and a 9-month school year. For purposes of analysis, the exposure data were also dichotomized by source type. Exposed individuals were those with any exposure to surface water; nonexposed persons were those who drank water only from groundwater sources that were shown to have little or no THM.

Analysis methods.—The association between $CHCl_3$ exposure and colorectal cancer was investigated in simple form by use of McNemar's matched-pair analysis (*18*) and the one-sided Wilcoxon signed rank statistic (*19*). We used both matched (*20*) and unmatched (*21*) linear logistic regression analyses to consider additional factors related to colorectal cancer including population density, marital status, age, and year of death. All analyses were performed for the 331 histologically confirmed cases separately, as well as for all 395 cases. The results were virtually identical, and only the total group analyses are shown here. Similarly, no appreciable differences were seen when the colon and rectal cancer cases were analyzed separately, and only the combined results are presented. Finally, only minor differences were detected between matched and unmatched logistic regression, and only the unmatched results are presented.

RESULTS

The results of matched-pair analysis, with exposure dichotomized by source type, are shown in table 2. For these results the odds ratio=1.07, the 90% confidence interval=0.79–1.43, and P=.68. There was no difference between cases and controls in the proportions who

TABLE 2.—*Exposure of 395 subjects and matched controls to water containing $CHCl_3$*

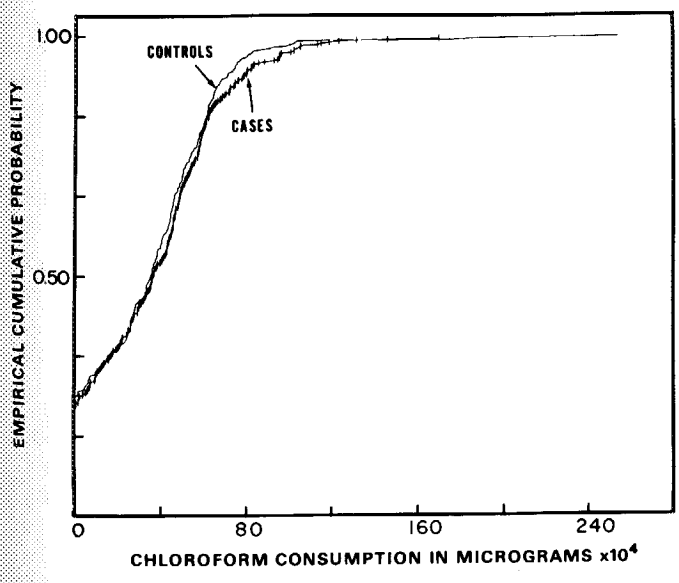
Case	Matched control	
	Exposed	Unexposed
Exposed	226	74
Unexposed	69	26

were never exposed to surface water sources (24% vs. 25%).

The cumulative $CHCl_3$ distribution function curves for cases and controls are shown in text-figure 1. The distribution of the case-control differences did not readily conform to normality, even after transformations and removal of outliers. Consequently, the nonzero differences were tested nonparametrically with the Wilcoxon test. No difference was detected (P=.60). For exposed cases the mean plus or minus standard error (n=305) was 463,180±265,062 mg; for exposed controls (n=297) it was 455,110±269,678 mg.

In addition to cumulative $CHCl_3$ exposure prior to death, we also examined pre-diagnostic exposure by cumulating estimated $CHCl_3$ consumption for both cases and controls from 20 years prior to death until the case's year of diagnosis. This procedure protected against a possible bias resulting from a difference between cases and controls in exposure after diagnosis that was not present before diagnosis. For example, migration to a metropolitan area for therapy might be expected to result in an increase in $CHCl_3$ exposure for cases that would not be seen for controls. Again, the Wilcoxon test failed to detect a difference between cases and controls (P=.28).

With the basic outcome-exposure analysis revealing no significant difference, linear logistic analysis was used to control for confounding and to explore for other potential associations.



TEXT-FIGURE 1.—Cumulative distribution function of 20-yr cumulative $CHCl_3$ exposure.

The relation between cancer outcome and cumulative $CHCl_3$ exposure was adjusted by the consideration of source type (0,1 indicator variables), the average source type (coded in increasing order of THM load: 1=lake, 2=stream or creek, 3=river, and 4=reservoir), dichotomized exposure (1 if chlorinated source and 0 otherwise), the population density for place of residence at time of death (from the 1970 census), marital status (ever married vs. never married), and the matching variables (age at death and yr of death) in an unconditional logistic regression. The likelihood ratio test statistic for this model compared to that for the same model without cumulative $CHCl_3$ was 0.047 (P=.83). The full model is listed in table 3.

None of the added explanatory variables was significantly associated with outcome. The variable with the highest association was average source type, though its standardized estimate of effect was only 1.41 (P=.16). The likelihood ratio test statistic for the model with the full set of explanatory variables versus that without average source type was 1.9869 (P=.16).

To look further for a chlorine by-product effect other than that due to $CHCl_3$, several other water treatment variables were modeled, including cumulative log chlorine dose, cumulative log chlorine residual, and various interaction terms. No significant associations were found. As a final analytic step, an exhaustive all-possible-subset regression was run that included all second-order interactions. The effect of these variables was investigated, in part, since these variables serve as potential surrogates for other chlorinated organics that may be stronger carcinogens (*22*). Again, no significant associations were discovered. This analysis included all linear combinations of the components of our $CHCl_3$ model. Thus our negative findings are not dependent on the particular model obtained independently by the regression analysis of $CHCl_3$ concentrations discussed in "Appendix."

DISCUSSION

We studied the relation of THM to colorectal cancer among deceased white women teachers with strict attention to potential sources of bias.

In our analysis we utilized both dichotomized exposure and continuous cumulative $CHCl_3$ exposure calculated from summer levels for the 20-year period prior

TABLE 3.—*Full unconditional logistic model*

Variable	Regression coefficient	Standardized estimate (N(0,1))
Constant	−0.617	−0.56
Cumulative $CHCl_3$	-0.654×10^{-7}	−0.216
Average source type[a]	0.090	1.41
Population density	0.304×10^{-5}	−0.15
Marital status	0.192	1.21
Age	0.002	0.27
Year of death	0.004	0.26

[a] 1=lake, 2=stream or creek, 3=river, and 4=reservoir.

to death. Since THM levels are known to be seasonal with the highest levels occurring in summer, the calculated THM concentrations possibly overestimate the cumulative exposure. Furthermore, negative correlation of other months with these summer levels could result in poor estimates of cumulative exposure. Nevertheless, a distinguishing feature of the present investigation is the quantitative manner in which exposure information was ascertained. Although the resulting 20-year cumulative THM variable is not without imperfections, it represents a clear improvement over the exposure variables used in previous investigations. The lack of significant association in the analysis with the dichotomized exposure variable was concordant with the results with the use of quantitative exposure estimates.

Several restrictions and exclusions were used to arrive at our final study population. None of these selection factors, however, has any obvious relation to exposure, making bias due to this procedure unlikely. Limiting the residence of the study cohort to the central corridor of the State, for example, may have reduced the variation in exposure (and thus reduced efficiency), but it should not have affected validity. We are unaware of any evidence in humans associating THM with cardiovascular disease or any of the other diagnoses among our control group. There are, however, limited indications of possible $CHCl_3$-induced heart and vascular lesions in animals (*23, 24*). Such an association, were it to exist in our study population, would tend to minimize any difference observed between cases and controls.

Misclassification of outcome was minimized by use of predominantly histologically confirmed cases of colorectal cancer. Controls had no tumor registry reports of any cancer. Exposure misclassification was similarly minimized by the collection of extensive records on home and work addresses and water treatment facilities. All information collected was objective and was of comparable quality for cases and controls.

Information was available on a number of variables reported to be related to colorectal cancer and potentially related to $CHCl_3$ exposure. These variables included water source type, population density (*25*), marital status (*26*), age (*27*), and year of death (*27*). In our study population none of these variables was significantly associated with outcome. Therefore, none altered the basic relation of $CHCl_3$ to colorectal cancer that we were evaluating. Many other chlorinated organics in drinking water, particularly the numerous nonvolatile compounds, are at levels too low for isolation. Ames testing (*28*) and tissue asssays (*22*) have demonstrated mutagenicity and promoting properties for drinking water concentrates. To the extent that $CHCl_3$ could serve as a marker for such compounds, no association with colon cancer risk was seen. However, if the formation of these compounds is not governed by chlorine dose and precursor interactions related to those seen for $CHCl_3$, an association with risk could be missed.

An unmeasured and potentially important risk factor for colorectal cancer is diet (*27*). For bias due to diet factors to be operational, however, an association between the diet and $CHCl_3$ in water would have to be present, which seems unlikely. In addition, we have no information on sources of exposure to $CHCl_3$ other than drinking water. Past use of cough syrups containing $CHCl_3$ might be a significant exposure, but bias would result only if cough syrup use was related to $CHCl_3$ in drinking water and if cough syrup was related to colorectal cancer.

Finally, potential confounding bias due to other unmeasured factors was generally minimized by the use of teachers as the study population. Teachers can be assumed to be similar with regard to many background variables, such as education, socioeconomic status, lack of hazardous physical or chemical exposures in the workplace, and access to medical care. This feature differentiates the current study from previous investigations in which the degree of homogeneity of the cases and controls was markedly less, and it provides a possible explanation of why our study does not reproduce previous results.

Although homogeneous with respect to background variables, the study population was unlikely to be homogeneous with respect to the exposure variable. Since teachers must serve communities throughout the State in approximate proportion to the student population, they have geographic and water source heterogeneity similar to that of the general population of the study corridor.

In summary, we found no evidence of a relation of THM to colorectal cancer in white women teachers in upstate New York. Additional analytical studies are needed to confirm this result and to study other cancer sites.

APPENDIX: STATISTICAL MODEL FOR CHLOROFORM ESTIMATION

A regression approach was utilized to develop a $CHCl_3$ estimation model based on data from a New York State Department of Health survey (*17*). The survey collected single grab-samples from 174 surface-source water systems. (Surveyed ground water systems showed negligible $CHCl_3$ formation.) Mean $CHCl_3$ concentration among the four source types in the survey increased linearly, producing the following rank ordering:

1) Lake (lowest)
2) Stream or creek
3) River
4) Reservoir

Survey data included effluent $CHCl_3$ concentration, pre-chlorine and post-chlorine dose, final chlorine residual, chlorine demand, pH, temperature, turbidity, color, contact time, and other chemical treatments.

The set of survey variables that best predicted $CHCl_3$ formation was determined by use of hierarchical and stepwise regression modeling. Logarithmic transforma-

tion of the dependent and some independent variables was employed to satisfy the regression assumptions of homoscedasticity, normal error distribution, and linearity (log transformation suggested by log-normal $CHCl_3$ distribution in several large surveys) (*17, 29, 30*). The selected variables were used to reanalyze the data with a new robust regression method, producing a final estimation equation for $CHCl_3$. The robust regression method is insensitive to the influence of outlier observations as well as self-critical; i.e., it individually assesses the probability of occurrence of each data point and weights it accordingly through reference to the assumed underlying distribution (*31*). A small percentage of outliers is common in surveys of this type and can produce biased estimates of regression parameters with conventional least squares methods.

The application of the robust regression estimation procedure detected ten outlier observations. Reexamination of these water systems and their data showed probable errors in eight of them. For example, in five of the ten, where flow meters were lacking, the chlorine dose was given in pounds per day rather than pounds per million gallons of water. When estimating the model parameters by least squares, removal of these ten outliers increased the R^2 from 0.33 to 0.54, indicating the large distortion they produce. A large component of the remaining variation is due to random day-to-day fluctuations in $CHCl_3$ levels; such fluctuations average out as an individual accumulates a 20-year $CHCl_3$ dose. The final least squares regression model was

$$\ln Y = 0.35 \ln X_1 + 0.41 \ln X_2 + 0.11 \ln X_3 + 2.59,$$

where Y=$CHCl_3$ concentration (μg/liter), X_1=prechlorine dose plus post-chlorine dose (pounds/million gallons), X_2=effluent chlorine residual plus 0.25 (μg/liter),[7] X_3=source type (1=lake, 2=stream, 3=river, and 4=reservoir), and R^2=0.54.

The source-type variable probably serves as a surrogate for the organic precursor content of raw water. We observed that the mean log of the $CHCl_3$ content increased nearly linearly with the logarithms of the rank ordering of source type. The use of indicator variables for source type did not significantly improve the model fit; thus the logarithm of rank order source type variable was selected for inclusion in the model.

Estimation of $CHCl_3$ exposure for individual study subjects involved substituting data from operation records of the given water system for the independent variables in the model. This substitution allowed estimates of cumulative $CHCl_3$ to be sensitive to changes in source of exposure and changes at a given source over time. Daily values of the variables for July and August were averaged and were used in the model as an average over the past year. Chlorine doses are typically highest in July and August, resulting in a conservative estimate of $CHCl_3$ risk. Rank correlation analysis of $CHCl_3$ levels at water systems in New York and Iowa (*32*) showed generally good correlation between summer and winter $CHCl_3$ rankings. This finding is not surprising inasmuch as chlorine dose and organic precursor level influence $CHCl_3$ formation more than does temperature (*33*) and exhibit trends that are relatively constant over the course of a year.

[7] *Note:* Correction factor 0.25 is added to avoid logarithm of zero.

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